# General

## Guideline Title

Health maintenance for people with sickle cell disease. In: Evidence-based management of sickle cell disease.

## Bibliographic Source(s)

Health maintenance for people with sickle cell disease. In: Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. p. 11-30.

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

# Regulatory Alert

## FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines : A U.S. Food and Drug Administration (FDA) review has found that the growing combined used of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

# Recommendations

## Major Recommendations

Definitions of the grades of recommendation (Strong, Weak), the quality of supporting evidence (High, Moderate, Low, Very Low), and consensus statements are presented at the end of the "Major Recommendations" field.

*Note from the National Heart, Lung, and Blood Institute (NHLBI) and the National Guideline Clearinghouse (NGC)*: The evidence-based management of sickle cell disease (SCD) has been divided into five topic areas with individual summaries covering recommendations to assist health care professionals in various aspects of patient management. In addition to the current summary, the following are available:

- Managing acute complications of sickle cell disease
- Managing chronic complications of sickle cell disease
- Hydroxyurea therapy in the management of sickle cell disease
- Blood transfusion in the management of sickle cell disease

Prevention of Invasive Pneumococcal Infection

Key Question 1

What are the benefits and harms of prophylactic antibiotic use in children with SCD? What are the recommended antibiotic administration regimens and schedules?

Recommendations

1. Administer oral penicillin prophylaxis (125 mg for age <3 years and 250 mg for age ≥3 years) twice daily until age 5 in all children with homozygous hemoglobin SS (HbSS). (Strong Recommendation, Moderate-Quality Evidence)
2. Discontinue prophylactic penicillin in children with HbSS at age 5 unless they have had a splenectomy or invasive pneumococcal infection. When discontinuing penicillin prophylaxis at age 5, it is important to assure that the child has completed the recommended pneumococcal vaccination series, and if not, complete the series immediately. (Weak Recommendation, Moderate-Quality Evidence)
3. Consider withholding penicillin prophylaxis from children with hemoglobin SC (HbSC) disease and HbS$\beta^+$-thalassemia unless they have had a splenectomy. (Weak Recommendation, Low-Quality Evidence)
4. Assure that people of all ages with SCD have been vaccinated against *Streptococcus pneumoniae*.* (Strong Recommendation, Moderate-Quality Evidence)
5. Remind people with SCD, their families, and caregivers to seek immediate medical attention whenever fever (temperature greater than 101.3°F or 38.5°C) occurs, due to the risk for severe bacterial infections. (Consensus–Panel Expertise)

*Refer to the "Immunization" section of this chapter in the original guideline document for comprehensive information on immunizations.

Screening for Renal Disease

Key Question 2

In asymptomatic individuals with SCD, what is the effect of screening for renal disease, by measuring serum creatinine and urine albumin and protein, on mortality and the development of end-stage renal disease (ESRD)?

Recommendation

1. Screen all individuals with SCD, beginning by age 10, for proteinuria. If the result is negative, repeat screening annually. If the result is positive, perform a first morning void urine albumin-creatinine ratio and if abnormal, consult with or refer to a renal specialist. (Consensus–Panel Expertise)

Screening for Pulmonary Hypertension (PH)

Key Question 3

In asymptomatic individuals with SCD, what is the effect of screening for PH on mortality and the development of future cardiac and pulmonary complications?

Recommendation

1. Based on the insufficient evidence, the expert panel was unable to make a recommendation for or against screening for PH. However, this does not diminish the importance of evaluating individuals who have symptoms or who have had abnormal echo testing.

Electrocardiogram (ECG) Screening

Key Question 4

In asymptomatic individuals with SCD, what is the effect of screening with ECG on mortality and the development of future cardiac disease?

Recommendation

1. Routine ECG screening is not recommended in children and adults with SCD. (Weak Recommendation, Low-Quality Evidence)

Screening for Hypertension (HTN)

Key Question 5

In people with SCD, what is the effect of screening for HTN on mortality, stroke, and heart disease? What are the acceptable limits for blood pressure parameters above which cardiovascular and cerebrovascular morbidity occur?

Recommendations

1. In adults with SCD, screen for HTN and treat to lower systolic blood pressure ≤140 and diastolic blood pressure ≤90 according to "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7). (Consensus–Adapted)
2. In children with SCD, measure blood pressure, and evaluate and treat HTN following recommendations from the NHLBI's "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents." (Consensus–Adapted)

Screening for Retinopathy

Key Question 6

In asymptomatic individuals with SCD, are dilated eye examinations useful, and, if so, with what frequency should they be done?

Recommendations

1. In people with SCD, refer to an ophthalmologist for a dilated eye examination to evaluate for retinopathy beginning at age 10. (Strong Recommendation, Low-Quality Evidence)
2. For people having a normal dilated retinal examination, re-screen at 1 to 2 year intervals. (Consensus–Panel Expertise)
3. Refer people with suspected retinopathy to a retinal specialist. (Consensus–Panel Expertise)

Screening for Risk of Stroke Using Neuroimaging

Key Question 7

In asymptomatic individuals with SCD, what is the effect of screening with neuroimaging tests (computed tomography [CT] scan, magnetic resonance imaging [MRI], or transcranial Doppler [TCD]) on the risk of stroke?

Recommendations

1. In children with sickle cell anemia (SCA) screen annually with TCD according to methods employed in the Stroke Prevention Trial (STOP) studies, beginning at age 2 and continuing until at least age 16. (Strong Recommendation, Moderate-Quality Evidence)
2. In children with conditional (170–199 cm/sec) or elevated (>200 cm/sec) TCD results, refer to a specialist with expertise in chronic transfusion therapy aimed at preventing stroke. (Strong Recommendation, High-Quality Evidence)
3. In children with genotypes other than SCA (e.g., HbS$\beta^+$-thalassemia or HbSC), do not perform screening with TCD. (Strong Recommendation, Low-Quality Evidence)
4. In asymptomatic children with SCD, do not perform screening with MRI or CT. (Moderate Recommendation, Low-Quality Evidence)
5. In asymptomatic adults with SCD, do not perform screening with neuroimaging (TCD, MRI, or CT). (Moderate Recommendation, Very Low-Quality Evidence)

Screening for Pulmonary Disease

Key Question 8

In asymptomatic individuals with SCD, what is the effect of screening with pulmonary function tests (PFTs) on cardiac and pulmonary complications?

Recommendations

1. In children and adults with SCD, assess for signs and symptoms of respiratory problems (such as asthma, chronic obstructive pulmonary disease [COPD], restrictive lung disease, or obstructive sleep apnea) by history and physical examination. (Consensus–Panel Expertise)
2. In children and adults with SCD found to have signs or symptoms of respiratory problems by history and/or physical examination, further assessment, which includes PFTs, is recommended to determine the cause and develop a plan to address the problem. (Consensus–Panel Expertise)
3. Do not screen asymptomatic children and adults with PFTs. (Moderate Recommendation, Low-Quality Evidence)

Reproductive Counseling

Evidence reviews on this topic were not performed by the methodology team. The expert panel based its recommendations on a review of the literature and consensus opinion.

Specific Recommendations for Women or Men with SCD

1. Encourage each woman, man, and couple affected by SCD to have a reproductive life plan. (Consensus–Panel Expertise)
2. As a part of primary care visits, provide risk assessment and educational and health promotion counseling (or refer to individuals with expertise in these disciplines) to all women and men of childbearing age to reduce reproductive risk and improve pregnancy outcomes. Provide contraceptive counseling, if desired, to prevent unintended pregnancy, and if pregnancy is desired, provide preconception counseling. (Consensus–Panel Expertise)
3. If the partner of a man or woman with SCD has unknown SCD or thalassemia status, refer the partner for hemoglobinopathy screening. (Consensus–Panel Expertise)
4. After testing, refer couples who are at risk for having a potentially affected fetus and neonate for genetic counseling. (Consensus–Panel Expertise)

Specific Recommendations for Women with SCD

1. Test women with SCD who have been transfused and are anticipating pregnancy for red cell alloantibodies. (Consensus–Panel Expertise)
2. If a woman has red cell alloantibodies, test her partner for the corresponding red cell antigen(s). (Consensus–Panel Expertise)
3. If the partner tests positive for the corresponding red cell antigen(s), counsel the woman and her partner about the risks of hemolytic disease in the fetus and neonate, how it is monitored, and how it is treated, or refer them to a maternal-fetal specialist who can provide this education. (Consensus–Panel Expertise)
4. Counsel women with SCD and their partners or refer for counseling about the following: (Consensus–Panel Expertise)
    a. Pregnancy in women with SCD is considered high risk, and there is an increased risk of adverse pregnancy outcomes including fetal (intrauterine) growth restriction, preterm delivery, and stillbirth.
    b. Additional fetal surveillance is required during a pregnancy.
    c. There are increased risks to a woman's health during pregnancy. These risks include an increased frequency of pain crises and an increased risk of thrombosis, infections, preeclampsia, and death relative to women who do not have SCD.

For women who require chronic opioid therapy during pregnancy, there is an increased risk of neonatal withdrawal in their newborns.

Contraception

Evidence reviews on this topic were not performed by the methodology team. Therefore, the expert panel based its recommendations on those developed by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC).

Recommendations

1. Progestin-only contraceptives (pills, injections, and implants), levonorgestrel intrauterine devices (IUDs), and barrier methods have no restrictions or concerns for use in women with SCD. (Consensus–Adapted)
2. If the benefits are considered to outweigh the risks, combined hormonal contraceptives (pills, patches, and rings) may be used in women with SCD. (Consensus–Adapted)

Clinical Preventive Services

Refer to Exhibit 5 in the original guideline document for the "Summary of U.S. Preventive Services Task Force's General Recommendations That Are Also Applicable to Persons with Sickle Cell Disease."

Immunizations

Key Question 9

Which immunizations should be given to people with SCD?

Recommendations

Evidence reviews on this topic were not performed by the methodology team. Therefore, the expert panel based its recommendations on those developed by the Advisory Committee on Immunization Practices (ACIP; see Exhibit 6 in the original guideline document).

1. All individuals with SCD should receive immunizations according to the ACIP harmonized immunization schedule unless they have a personal contraindication as noted in the ACIP schedule. (Consensus–Adapted)
2. Because of their increased susceptibility to invasive pneumococcal disease, all infants with SCD should receive the complete series of the 13-valent conjugate pneumococcal vaccine series beginning shortly after birth and the 23-valent pneumococcal polysaccharide vaccine at age 2 years, with a second dose at age 5 years. (Consensus–Adapted)

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Recommendations

| Grade of Recommendation | Clarity of Risk/Benefit | Quality of Supporting Evidence | Implications |
|---|---|---|---|
| **Strong recommendation**<br><br>**High-quality evidence** | Benefits clearly outweigh harms and burdens, or vice versa | Consistent evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies* | Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect. |
| **Strong recommendation**<br><br>**Moderate-quality evidence** | Benefits clearly outweigh harms and burdens, or vice versa | Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies | Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on confidence in the estimate of effect and may change the estimate. |
| **Strong recommendation**<br><br>**Low-quality evidence** | Benefits clearly outweigh harms and burdens, or vice versa | Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence | Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. |
| **Strong recommendation**<br><br>**Very low-quality evidence (very rarely applicable)** | Benefits clearly outweigh harms and burdens, or vice versa | Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence | Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain. |
| **Weak recommendation**<br><br>**High-quality evidence** | Benefits closely balanced with harms and burdens | Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies | The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change confidence in the estimate of effect. |
| **Weak recommendation**<br><br>**Moderate-quality evidence** | Benefits closely balanced with harms and burdens | Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies | Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and may change the estimate. |
| **Weak recommendation**<br><br>**Low-quality evidence** | Uncertainty in the estimates of benefits, harms, and burdens; benefits may be closely balanced with harms and | Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence | Other alternatives may be equally reasonable. Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. |

| Grade of Recommendation | Clarity of Risk/Benefit | Quality of Supporting Evidence | Implications |
|---|---|---|---|
| Weak recommendation | Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens | Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence | Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain. |
| **Very low-quality evidence** | | | |

*Source*: Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med*. 2006 Sep 1;174(5):605-14. Official Journal of the American Thoracic Society.

*Exceptionally strong evidence from unbiased observational studies includes: (1) evidence from studies that yield estimates of the treatment effect that are large and consistent; (2) evidence in which all potential biases may be working to underestimate an apparent treatment effect, and therefore, the actual treatment effect is likely to be larger than that suggested by the study data; and (3) evidence in which a dose-response gradient exists.

Consensus Statements

The panel believed that, for this guideline document to be most helpful to primary care providers and specialty health care professionals, it needed to be comprehensive. This required that, in areas with minimal existing direct evidence, the panel would provide recommendations based on their and others' expert opinions. Those recommendations are labeled as "consensus." Several different situations, outlined below, led to the use of consensus statements.

Consensus–Panel Expertise

- Systematic reviews conducted by the methodology team revealed minimal or no supporting evidence (e.g., management of acute hepatic sequestration).
- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with SCD presenting with fever or worsening anemia).
- Recommendations were based on the panel's expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain).

Consensus–Adapted

- These recommendations were based on the panel's expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD). The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

- Sickle cell disease (SCD) and SCD complications
  - Invasive pneumococcal infection
  - Renal disease
  - Pulmonary hypertension (PH)
  - Abnormalities such as prolonged corrected QT interval (QTc), ST-T segment abnormalities, and electrocardiographic cardiac enlargement
  - Hypertension (HTN)
  - Retinopathy
  - Stroke

        - Pulmonary disease
        - Preconception health
        - Vaccine-preventable illnesses
    - Unintended pregnancy in SCD
    - General health in SCD

## Guideline Category

Counseling

Management

Prevention

Risk Assessment

Screening

## Clinical Specialty

Cardiology

Emergency Medicine

Family Practice

Hematology

Infectious Diseases

Internal Medicine

Medical Genetics

Nephrology

Neurology

Nursing

Obstetrics and Gynecology

Ophthalmology

Pediatrics

Preventive Medicine

Pulmonary Medicine

Radiology

## Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

## Guideline Objective(s)

- To synthesize the available scientific evidence on sickle cell disease (SCD) and offer guidance to busy primary care clinicians
- To help people living with SCD receive appropriate care by providing the best science-based recommendations to guide practice decisions
- To assist health care professionals in the management of common issues, including routine health maintenance, the recognition and treatment of common acute and chronic complications and comorbidities of SCD, as well as the indications for and monitoring of hydroxyurea and blood transfusion therapy
- To help provide the latest evidence-based recommendations to manage this condition and to help engage health care professionals in supporting their implementation at the practice level
- To review the available evidence for health maintenance and screening and make recommendations for children and adults with SCD

## Target Population

Infants, children, adolescents, and adults with sickle cell disease (SCD)

## Interventions and Practices Considered

1. Prevention of invasive pneumococcal infection though prophylactic antibiotic (penicillin) use
2. Screening for renal disease by measuring serum creatinine and urine albumin and protein
3. Screening for pulmonary hypertension (PH; no recommendation made)
4. Electrocardiogram screening (routine screening not recommended)
5. Screening for hypertension (HTN)
6. Screening for retinopathy
7. Neuroimaging (computed tomography [CT] scan, magnetic resonance imaging [MRI], or transcranial Doppler [TCD]) to screen for stroke
8. Screening for pulmonary disease using pulmonary function tests (PFTs), history, and physical examination
9. Reproductive counseling
10. Contraception
11. General clinical preventive services
12. Immunizations

## Major Outcomes Considered

- Incidence of relevant infections
- Incidence of relevant mortality
- Incidence of adverse effects of prophylactic antibiotics
- Development of acute and chronic complications
- Diastolic, systolic, and mean blood pressure
- Prognosis of hypertension (HTN)
- Cardiovascular and cerebrovascular outcomes
- Blood pressure control

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

General Literature Search

Due to the comprehensive scope of the guidelines, the search strategies for the systematic reviews were designed to have high sensitivity and low specificity; hence, the strategies were often derived from population and condition terms (e.g., people with sickle cell disease [SCD] who have priapism) and not restricted or combined with outcome or intervention terms. To be inclusive of the available literature in the field, searches included randomized trials, nonrandomized intervention studies, and observational studies. Case reports and small case series were included only when outcomes involved harm (e.g., the adverse effects of hydroxyurea) or when rare complications were expected to be reported.

Literature searches involved multiple databases (e.g., Medline® In-Process & Other Non-Indexed Citations, MEDLINE®, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature [CINAHL®], TOXLINE®, and Scopus) and used controlled vocabulary (prespecified) terms supplemented with keywords to define concept areas.

An updated search was performed to span the time from June 1, 2010 through July 11, 2014.

Guideline-specific Literature Search

A comprehensive study of several databases was conducted, and all human studies in English published from January 1970 to December 2010 that addressed each Patient, Intervention, Comparison, Outcomes, and Study Design (PICOS) question were identified. In the specific instances of antibiotic therapy and blood pressure screening, the review began from database inception through January and July 2011, respectively. In the case of screening, the review went through July 2010. Meta-analysis was only feasible in two areas: (1) efficacy of antibiotic prophylaxis in children and (2) hypertension (HTN) in SCD. The topics of reproductive counseling, contraception, clinical preventive health care services, and immunizations were not searched; recommendations were derived from guidelines published by professional organizations that were based on systematic reviews of broader population groups; these recommendations are labeled "Consensus–Adapted."

Detailed information on the search questions, search strategy, study selection process, and list of excluded studies used in this guideline can be found in the systematic reviews (see the "Availability of Companion Documents" field).

## Number of Source Documents

General Literature Search

The initial literature searches performed to support these guidelines yielded 12,532 references. The expert panel also identified an additional 1,231 potentially relevant references. An updated search of randomized controlled trials (RCTs) added eight trials. All abstracts were reviewed independently by two reviewers using an online reference management system (DistillerSR—http://systematic-review.net ) until reviewers reached adequate agreement (kappa ≥0.90). A total of 1,575 original studies were included in the evidence tables.

Guideline-specific Literature Search

A total of 313 studies were included.

## Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

See the "Rating Scheme for the Strength of the Recommendations" field.

## Methods Used to Analyze the Evidence

Meta-Analysis

# Description of the Methods Used to Analyze the Evidence

General Methodology

Evidence Synthesis

Methodologists developed evidence tables to summarize individual study findings and present the quality of evidence (i.e., confidence in the estimates of effect). The tables included descriptions of study population, sickle cell disease (SCD) genotypes, interventions, and outcomes. Additional methodological details are discussed in each evidence table, including the search question, search strategy, study selection process, and list of excluded studies (see the "Availability of Companion Documents" field).

Evidence Framework

The methodology team used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to grade the quality of evidence, and, in concert with the panel, determine the strength of recommendations. The GRADE framework is accepted by more than 75 national and international organizations (see exhibit 3 in the original guideline document). It provides the advantages of: (a) separately judging the quality of supporting evidence and strength of recommendations, and (b) incorporating factors other than evidence in decisionmaking (e.g., the balance of benefits and harms; the perceived values and preferences of those with SCD; resources; and clinical and social context). GRADE emphasizes the use of patient-important outcomes (i.e., outcomes that affect the way patients feel, function, or survive) over laboratory and physiologic outcomes.

Determining Evidence Quality

In the GRADE framework, the quality of evidence (in this case, the body of evidence) is rated as high, moderate, low, or very low. The quality of evidence derived from randomized trials starts as "high," and the quality of evidence derived from observational studies starts as "low." The quality of evidence can then be lowered due to methodological limitations in individual studies (risk of bias), inconsistency across studies (heterogeneity), indirectness (the extent to which the evidence fails to apply to the specific clinical question in terms of the patients, interventions, or outcomes), imprecision (typically due to a small number of events or wide confidence intervals), and the presence of publication and reporting biases. Conversely, the quality of evidence can be upgraded in certain situations such as when the treatment effect is large or a dose-response relationship is evident.

Existing Systematic Reviews and Clinical Practice Guidelines

The expert panel and methodology team identified existing systematic reviews and clinical practice guidelines that were relevant to the topics of this guideline, even though they were not necessarily specific to people with SCD. If the methodological quality of these resources was found to be appropriate by the methodology team, they were used. Using this external evidence was considered helpful because well-conducted systematic reviews made the process of identifying relevant studies more feasible. In addition, using existing guidelines developed by professional organizations enabled the panel to develop more comprehensive recommendations that addressed specific aspects of care in individuals with SCD. Usually, this external evidence was derived from studies in non-sickle cell patient cohorts because it was felt that they offered more precise and useful inferences than evidence derived from sickle cell patient studies. For example, comparative evidence in the area of pain management in people with SCD was sparse. In this situation, pain management guidelines from individuals with other pain-related conditions proved to be helpful.

The methodology team used the AMSTAR tool to assess the methodological quality of systematic reviews. Recent well-conducted systematic reviews were identified that addressed hydroxyurea therapy in pediatric and adult patients. The expert panel and methodology team appraised these reviews and conducted additional searches to update the existing systematic review through May 2010 to find evidence for the benefits, harms, and barriers of using hydroxyurea. Regarding the management of children with SCD complications, the panel also used recent evidence that had been systematically reviewed.

Existing clinical practice guidelines were considered acceptable if they had prespecified clinical questions, were developed after a comprehensive literature search, had explicit and clear criteria for the inclusion of evidence, and included recommendations that were explicitly linked to the quality of supporting evidence. The expert panel and methodology team used relevant recommendations from the U.S. Preventive Services Task Force (USPSTF), the Advisory Committee on Immunization Practices (ACIP), the Centers for Disease Control and Prevention's (CDC) adaptation of the World Health Organization's (WHO) "Medical Eligibility Criteria for Contraceptive Use," and the American Pain Society's "Guideline for the Management of Acute and Chronic Pain in Sickle-Cell Disease," and "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain."

Guideline-specific Methodology

Meta-analysis was only feasible in two areas: (1) efficacy of antibiotic prophylaxis in children and (2) hypertension (HTN) in SCD.

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the evidence tables for this guideline (see the systematic reviews in the "Availability of Companion Documents" field).

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

These guidelines were developed by an expert panel composed of health care professionals with expertise in family medicine, general internal medicine, adult and pediatric hematology, psychiatry, transfusion medicine, obstetrics and gynecology, emergency department nursing, and evidence-based medicine. Panel members were selected by the National Heart, Lung, and Blood Institute's (NHLBI's) leadership.

Process and Methodology

The expert panel first convened in the spring of 2009 to establish the vision and purpose of the panel, discuss the process and schedule for producing the guidelines, and determine the critical areas to be addressed. Prior to this meeting, the expert panel participated in a conference call to introduce the panel's work and discuss the overarching questions that should be answered by the guidelines. Before beginning the writing of the guidelines report, the expert panel divided its work into sections dealing with preventive care or health maintenance, recognition and management of acute sickle-cell disease (SCD)-related complications, recognition and management of chronic SCD-related complications, and the two most broadly assessed and available disease-modifying therapies for SCD, hydroxyurea and chronic blood transfusions.

With the assistance of the methodology team and the supporting evidence center, the panel then developed key questions and literature search terms to identify evidence. The field of SCD has a limited number of randomized controlled trials (RCTs) or large prospective cohort studies to guide clinical decisionmaking; therefore, few of the recommendations in this document are based on this highest quality evidence. For common health issues, the panel included the evidence-based recommendations of the United States Preventive Services Task Force (USPSTF) as well as vetted recommendations of other groups. These recommendations include the SCD reproductive-related recommendations of the World Health Organization (WHO), the immunization recommendations of the Advisory Committee on Immunization Practices (ACIP), and the acute and chronic pain management recommendations of the American Pain Society (APS). These recommendations are denoted as "Consensus–Adapted."

Recognizing the need to provide practical guidance for common problems that may lie outside of the panel's evidence reviews or available science, in many areas the published evidence was supplemented by the expertise of the panel members, who have many years of experience in managing and studying individuals with SCD. Recommendations based on the opinions of the expert panel members are labeled as "Consensus–Panel Expertise." Each is clearly labeled with the strength of the recommendation and the quality of evidence available to support it.

Determining the Strength of Recommendations

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework rates the strength of recommendations as "strong" or "weak." However, the panel modified the GRADE system and used a third category—moderate—when they determined that patients would be better off if they followed a recommendation, despite there being some level of uncertainty about the magnitude of benefit of the intervention or the relative net benefit of alternative courses of action. The panel intends for these moderate-strength recommendations to be used to populate protocols of care and provide a guideline based on the best available evidence. The panel does not intend for weak- or moderate-strength recommendations to generate quality-of-care indicators or accountability measures or affect insurance reimbursement. Variation in care in the areas of weak- or moderate-strength recommendations may be acceptable, particularly in ways that reflect patient values and preferences. Conversely, strong recommendations represent areas in which there is confidence in the evidence supporting net benefit, and the recommendations likely apply to most individuals with sickle cell anemia. For more information, see the "Rating Scheme for the Strength of the Recommendations" field.

## Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Recommendations

| Grade of Recommendation | Clarity of Risk/Benefit | Quality of Supporting Evidence | Implications |
|---|---|---|---|
| **Strong recommendation**<br><br>**High-quality evidence** | Benefits clearly outweigh harms and burdens, or vice versa | Consistent evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies* | Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect. |
| **Strong recommendation**<br><br>**Moderate-quality evidence** | Benefits clearly outweigh harms and burdens, or vice versa | Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies | Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on confidence in the estimate of effect and may change the estimate. |
| **Strong recommendation**<br><br>**Low-quality evidence** | Benefits clearly outweigh harms and burdens, or vice versa | Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence | Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. |
| **Strong recommendation**<br><br>**Very low-quality evidence (very rarely applicable)** | Benefits clearly outweigh harms and burdens, or vice versa | Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence | Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain. |
| **Weak recommendation**<br><br>**High-quality evidence** | Benefits closely balanced with harms and burdens | Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies | The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change confidence in the estimate of effect. |
| **Weak recommendation**<br><br>**Moderate-quality evidence** | Benefits closely balanced with harms and burdens | Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies | Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and may change the estimate. |
| **Weak recommendation**<br><br>**Low-quality evidence** | Uncertainty in the estimates of benefits, harms, and burdens; benefits may be closely balanced with harms and burdens | Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence | Other alternatives may be equally reasonable. Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. |
| **Weak recommendation**<br><br>**Very low-quality evidence** | Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens | Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence | Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain. |

*Source*: Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med.* 2006 Sep 1;174(5):605-14. Official Journal of the American Thoracic Society.

*Exceptionally strong evidence from unbiased observational studies includes: (1) evidence from studies that yield estimates of the treatment effect that are large and consistent; (2) evidence in which all potential biases may be working to underestimate an apparent treatment effect, and therefore, the actual treatment effect is likely to be larger than that suggested by the study data; and (3) evidence in which a dose-response gradient exists.

Consensus Statements

The panel believed that, for this guideline document to be most helpful to primary care providers and specialty health care professionals, it needed to be comprehensive. This required that, in areas with minimal existing direct evidence, the panel would provide recommendations based on their

and others' expert opinions. Those recommendations are labeled as "consensus." Several different situations, outlined below, led to the use of consensus statements.

Consensus–Panel Expertise

- Systematic reviews conducted by the methodology team revealed minimal or no supporting evidence (e.g., management of acute hepatic sequestration).
- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with sickle cell disease [SCD] presenting with fever or worsening anemia).
- Recommendations were based on the panel's expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain).

Consensus–Adapted

- These recommendations were based on the panel's expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD). The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

### Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

### Method of Guideline Validation

External Peer Review

Internal Peer Review

### Description of Method of Guideline Validation

Prior to publication, these guidelines were reviewed by the National Heart, Lung, and Blood Institute (NHLBI) Advisory Council, a separate panel of sickle cell disease (SCD) experts, and the National Blood Disorders Program Coordinating Committee. The guidelines were also posted to the NHLBI Web site for an extensive public review and comment period, which resulted in the submission of more than 1,300 comments from individuals and professional societies. The expert panel and NHLBI staff reviewed each comment or recommendation, many of which resulted in a revision to the guidelines. The guidelines were then reviewed by SCD experts representing three professional societies.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Screening may help to identify risk factors and early signs of complications in order to implement measures to reduce morbidity and mortality in individuals with sickle cell disease (SCD).

### Potential Harms

Intrauterine devices (IUDs) and intrauterine implants carry modest risks associated with the insertion procedure, while sterilization carries risks associated with the surgical procedure. There is no evidence that IUDs pose an increased risk for women with sickle cell disease (SCD).

## Contraindications

### Contraindications

- Women with sickle cell disease (SCD) may have additional considerations that need to be taken into account when assessing the safety of contraceptive methods. For example, a history of stroke is a contraindication to combined hormonal contraception, and by age 20, approximately 11 percent of untreated women with SCD have had a clinically apparent stroke; this statistic increases to 24 percent by age 45.
- The expert panel notes that current maternal use of hydroxyurea is a contraindication to breastfeeding.

## Qualifying Statements

### Qualifying Statements

The purpose of the "Evidence-Based Management of Sickle Cell Disease: Expert Panel Report (EPR), 2014" is to synthesize the available scientific evidence on sickle cell disease and offer guidance to busy primary care clinicians. Readers of this report should remember that this document is intended to provide guidance for management, not to be rigidly prescriptive. The panel recognizes that the responsible clinician's judgment regarding the management of patients remains paramount. Therefore, the Expert Panel Report is a tool to be adopted and implemented in local and individual settings, and to provide an opportunity for shared decisionmaking in which providers and patients are both fully engaged.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

### Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Living with Illness

Staying Healthy

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

Health maintenance for people with sickle cell disease. In: Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. p. 11-30.

## Adaptation

- In developing consensus recommendations for screening for hypertension, the panel adapted recommendations from "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" and the NHLBI report "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents":
  - Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-52.
  - National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 Suppl 4th Report):555-76.
- The Centers for Disease Control and prevention (CDC) adapted the World Health Organization (WHO)'s "Medical Eligibility Criteria for Contraceptive Use" for women with sickle cell disease, and those criteria are the basis for the panel's recommendations on contraception:
  - Centers for Disease Control and Prevention. U.S. Medical Eligibility Criteria for Contraceptive Use, 2010—Adapted from the World Health Organization Medical Eligibility Criteria for Contraceptive Use, 4th edition. *MMWR Recomm Rep*. 2010;59(RR–4):1-86.
- The expert panel adapted its recommendations for immunizations from those made by the Advisory Committee on Immunization Practices (ACIP):
  - Ahmed F, Temte JL, Campos-Outcalt D, Schunemann HJ; ACIP Evidence Based Recommendations Work Group (EBRWG). Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC). *Vaccine*. 2011;29(49):9171-6.

## Date Released

2014

## Guideline Developer(s)

National Heart, Lung, and Blood Institute (U.S.) - Federal Government Agency [U.S.]

## Source(s) of Funding

United States Government

## Guideline Committee

Expert Panel

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Refer to the original guideline document for members of the National Heart, Lung, and Blood Institute staff and the contractor support.

## Financial Disclosures/Conflicts of Interest

The National Heart, Lung, and Blood Institute (NHLBI) established the expert panel and invited the panel members. All members served as volunteers and received no compensation from NHLBI or any other entity for their participation.

During the development of these guidelines, measures were taken to ensure the transparency of the evidence review process and to manage all potential or perceived conflicts of interest. At the initial expert panel meeting, expert panel members were asked by the panel co-chairs to disclose interests and relationships that could potentially influence their participation or pose a potential conflict of interest. The responses are provided below.

- Araba N. Afenyi-Annan, M.D., M.P.H.—Consultant, Transfusion Safety Summit: Risks Associated with Iron Toxicity in Transfusional Medicine—Novartis Pharmaceuticals Corporation (November 2008); Duke University Comprehensive Sickle Cell Center, Mentored Research Training Supplement (April 2005–April 2006); Expert Witness for Hall, Booth, Smith & Slover, P.C. (2010–present)
- Samir K. Ballas, M.D.—Speaker's Bureau, Novartis; Sickle Cell Advisory Board, HemaQuest; U.S. Sickle Cell Advisory Board, Sangart
- Kathryn L. Hassell, M.D.—Advisory Board, ApoPharma; Consultant, AGA Medical Corp.; Consultant and Principal Investigator of Local Site Multicenter Sickle Cell Study, Terumo, Inc.; Principal Investigator of Local Site Multi-Center Sickle Cell Study, GlycoMimetics, Inc.; Principal Investigator of Local Site Multi-Center Sickle Cell Study, Emmaus, Inc.; Board of Directors, Mount Evans Home Health & Hospice; Medical Advisory Board, Foundation for Women and Girls with Blood Disorders; Medical Advisory Board, PFO Research Foundation
- Andra H. James, M.D., M.P.H.—Consultancy for the von Willebrand Disease Medical Advisory Board for CSL Behring; Research study of antithrombin levels in pregnancy for Grifols/Talecris; Study of von Willebrand factor levels and fibrinogen levels post partum for CSL Behring; Expert witness for Johnson & Johnson and Sanofi-Aventis
- Lanetta Jordan, M.D., M.P.H., M.S.P.H.—National Heart, Lung, and Blood Advisory Council; Faculty Chair, Sickle Cell Disease Association of America, Inc. (SCDAA) and National Initiative for Children's Healthcare Quality (NICHQ) for Health Resources and Services Administration-funded Sickle Cell Disease Treatment Demonstration Program; AESRx Medical Advisory Council; Prolong Pharmaceutical Medical Advisory Board; Consultant for NKT Therapeutics, TriStem, Pfizer, and Novartis; Board Member, Foundation for Women and Girls with Blood Disorders and Miami YWCA
- Sophie M. Lanzkron, M.D., M.H.S.—Scientific Advisory Board for HemaQuest; Principal investigator on studies sponsored by Emmaus, GlycoMimetics, Inc., and Novartis
- Paula J. Tanabe, Ph.D., R.N., M.S.N., M.P.H.—Partner, ESI Triage Research Team, LLC; Principal investigator on Agency for Healthcare Research and Quality research grant; Subcontractor to the Michigan Public Health Institute and the Health Resources and Services Administration (HRSA) to conduct a project in SCD, pediatrics, emergency department (ED) research; recipient of Duke School of Nursing grant to complete a project to measure the effect of a high dose opioid protocol to treat adults with a vaso-occlusive crisis (VOC) in the ED; Expert witness consultant on one SCD legal case
- Russell E. Ware, M.D., Ph.D.—Consultant for Bayer, Novartis Pharmaceuticals, and Sobi

No relationships to disclose: George R. Buchanan, M.D.; Richard Lottenberg, M.D.; William J. Savage, M.D., Ph.D.; Barbara P. Yawn, M.D., M.Sc., M.S.P.H.

## Guideline Endorser(s)

American Academy of Emergency Medicine - Medical Specialty Society

American Academy of Pediatrics - Medical Specialty Society

American Academy of Physician Assistants - Professional Association

American Osteopathic Association - Professional Association

American Society of Hematology - Medical Specialty Society

American Society of Pediatric Hematology/Oncology - Professional Association

International Association of Sickle Cell Nurses and Physician Assistants - Professional Association

National Black Nurses Association, Inc - Professional Association

National Institute for Children's Health Quality - Professional Association

National Medical Association - Professional Association

Sickle Cell Disease Association of America - Disease Specific Society

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Electronic copies: Available from the National Heart, Lung, and Blood Institute (NHLBI) Web site .

Print copies: Available from the NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbiic@dgsys.com.

## Availability of Companion Documents

The following are available:

- Evidence-based management of sickle cell disease. Expert panel report quick guide. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. 45 p. Electronic copies: Available from the National Heart, Lung, and Blood Institute (NHLBI) Web site .
- Management of sickle cell disease. Summary of the 2014 evidence-based report by expert panel members. JAMA. 2014 Sep 10;312(10):1033-1048. Electronic copies: Available from the Journal of the American Medical Association (JAMA) Network Web site .
- Elraiyah T, Nabhan M, Hazem A, LeBlanc A, Prokop L, Montori VM, Murad MH. The use of prophylactic antibiotic therapy in children with sickle cell disease: a systematic review and meta-analysis, 2012. 20 p. Electronic copies: Available from the NHLBI Web site .
- Mullan RJ, Lane M, Hazem A, Prokop L, Montori VM, Murad MH. Blood pressure and sickle cell disease: a systematic review and meta-analysis, 2012. 36 p. Electronic copies: Available from the NHLBI Web site .
- Nabhan M, Hazem A, Elraiyah T, Elamin M, Mullan R, Prokop L, Montori VM, Murad MH. The use of screening tests in patients with sickle cell disease: a systematic review, 2012. 188 p. Electronic copies: Available from the NHLBI Web site .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on October 24, 2014. This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on opioid pain medicines. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines.

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